Research Article

Treatment of spasticity in spinal cord injury with botulinum toxin

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Context: Spasticity is one of the most frequent complications in spinal cord injury (SCI), and is routinely managed with oral pharmacologic therapy. Botulinum toxin (BT) is not accepted as a treatment for spasticity in SCI in Spain but may be used in certain cases of focal distribution.
Objective: To report the results with BT for treatment of spasticity in SCI.
Design and Setting: Descriptive retrospective study conducted at a specialist SCI rehabilitation center in Spain, covering patients first treated from 2012 through 2014, and successfully followed up for a minimum of 1 year. Data were collected on the following variables: demographic and SCI characteristics (level and grade); nature of spasticity, e.g. tone, distribution, spasms, articular involvement and pain; function; application of BT; tolerance and adverse reactions.
Results: The study covered 90 patients, predominantly male with incomplete injuries. Improvement in tone as measured by the modified Ashworth scale was a mean of 1.17 points. Goniometric improvement was achieved in 65.6% and improvement in pain in 38.9% of cases. There were no adverse side-effects.

Patients with focal spasticity showed a significantly greater improvement in tone ($P < 0.0001$). The earlier the BT injection, the greater the improvement in goniometric performance ($P < 0.006$) and pain ($P < 0.033$), with the best results being obtained within the first 6 months of clinical course. ASIA D injuries showed a greater improvement in tone ($P < 0.0001$).
Conclusions: BT can be both an effective treatment for focal spasticity in SCI and a good coadjuvant for oral treatments in generalized spasticity.

Keywords: Spasticity, Spinal cord injury, Botulinum toxin, Off-label

Introduction

Spasticity is one of the most frequent complications in spinal cord injury (SCI), with its incidence being estimated at over 65-70% of cases across the disorder's clinical course.[1–2] Spasticity is classically defined as hyperactivity of the myotatic reflex arc (stretch reflex) which gives rise to a velocity-dependent increase in resistance offered by muscles to passive stretching, and is caused by a lesion at any level of the pyramidal tract.[3] Currently, spasticity is understood to mean the association between this muscle hypertonia and other phenomena, such as spasms, clonus, hyper-reflexia and muscle coactivation, which accompany upper motor neuron lesions;[4] indeed it is these phenomena that predominate in the context of SCI.[5–8] Their assessment should include some measure of muscle tone (with the modified Ashworth scale/MAS being generally recommended), quantification of phasic phenomena (Penn Spasm Frequency Scale/PSFS) and measures of the repercussions of spasticity at an articular (goniometry), muscular (muscle testing) and functional level (specific scales of function and disability, quality of life, and subjective patient assessment),[1,9–11] though such evaluation can never be simplified by taking into account just one of the items, e.g. tone.[12] In SCI, spasticity is characterized by predominant involvement of the phasic components of muscle stretch reflex, and by being diffuse or generalized, with its most frequent manifestation being extensor spasms of the lower extremities.[5,6,13] Factors have been described that can increase the intensity or exacerbate the symptomatology

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of phasic spasticity, particularly neurogenic bowel dysfunction, bladder hyper-reflexia, anxiety, supine position and transfers.[14] Spasticity seems to be more prevalent in complete SCI, yet greater interference with activities of daily living, higher levels of pain, and more functional problems are classically described in incomplete SCI,[7,15] so that these patients may in fact report worse satisfaction with their lives because of spasticity rather than the injury as such, no matter how severe the latter might be.[16] Spasticity is only treated if it genuinely causes a problem of some kind. After controlling for aggravating factors, the principal treatment is pharmacologic, since the effect of physical treatment tends to be short-lived.[6,7,17] Due to its mechanism of action and efficacy, the medication of choice is oral baclofen,[7,15,18] though an important lack of adherence is described in standard treatments in SCI.[19] Hence, the main approach focuses on controlling aggravating factors ("noxious stimuli"), physical therapy, and systemic pharmacologic treatment.[6,7]

Botulinum toxin serotype A (BoNT/A) is produced by the *Clostridium botulinum* bacterium, and is a metalloprotease which, in nerve endings, proteolitically cleaves synaptosomal associated protein (SNAP-25) to inhibit the fusion of the synaptic vesicle with the presynaptic membrane of the axon terminal, and thus ultimately relax the muscle.[20] By injecting BoNT/A into certain muscles, local muscular hyperactivity can thus be reduced without affecting other muscles, thereby improving function and preventing deformities, which is why its use would be indicated in focal spasticity.[21] BoNT is estimated to reach the neuromuscular junction within 12 hours and the anterior horn within 24 hours of injection, and studies show that an effect is produced after 4 days, with the duration of the effect varying from 3 to 6 months.[22] BoNT/A is marketed in Spain in 2 forms which contain the neurotoxin and non-toxic proteins that make up the BoNT complex (onabotulinum and abobotulinum), and another form which exclusively contains the pure monomeric neurotoxin free of complexing proteins (incobotulinum).[20,23] BoNT is a drug indicated in focal spasticity, and approved by a number of institutions (Spanish Medication Agency; US Food and Drug Administration) for treatment of spasticity due to neurologic diseases such as cerebral palsy or stroke.[9,24,25] Its indication in SCI has not yet been officially proposed and there is very little literature on its use.

Accordingly, this study sought to describe the effects achieved by us with BoNT injections in patients with SCI.

Material and methods

A retrospective descriptive study was conducted at a specialist SCI rehabilitation center which provides health care to SCI patients from 8 of Spain's Autonomous Regions (*comunidades autónomas*) and is, additionally, regarded as a national referral center for complex SCI cases. The Rehabilitation Department has a Botulinum Toxin Unit staffed by 3 rehabilitation specialists tasked with evaluating patients with spasticity, and treating them with BoNT. The study covered all acute or chronic patients over age 18 years first treated with BoNT at our unit from 2012 through 2014 and successfully followed up for a minimum of 1 year.

Data were collected on the following variables:

- Demographic and injury characteristics, including neurologic level and American Spinal Injury Association (ASIA) grade according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)-ASIA.[26]
- Outcome measures: type of spasticity (predominantly tonic, phasic or mixed; generalized or focal), intensity measured using the MAS, and frequency of spasms as per the PSFS. To compare muscle tone results, we summed and calculated the arithmetic mean of the MAS scores (range 1-4) of the muscles assessed, in line with other spasticity studies.[27]
- Previous and concomitant treatments for spasticity, whether pharmacologic or otherwise.
- Changes in tone, goniometry and function. In the muscle tone study, we calculated the arithmetic mean of the MAS scores for the muscles injected, at baseline and again at one month of injection, and assessed the differences in score. We assessed function using the Spinal Cord Independence Measure (SCIM III) scale,[28] and determined whether there had been any goniometric and functional improvement. Patients were assessed both for pain, and to ascertain whether or not this had improved post-injection. Furthermore, we evaluated the duration of these effects after each injection and their persistence across repeated treatments. Patients' opinions about the effectiveness of the treatment were measured using a 4-point Personal Global Impression of Change scale, scored from 0 "no change" to 4 "excellent improvement".[29] For statistical study purposes, these categories were collapsed into 0 "no change", 1-2 "limited change", and "3- 4 excellent results".
- BoNT treatment protocol, i.e. treatment goals, muscles injected and location, and dosage. At our unit, we routinely administer the 3 types of BoNT indiscriminately (across the study period, incobotulinum was used on only 2 patients due to its lack of availability at our

Table 1 Patient sample demographics: neurological level and severity grade according with the ISNCSCI, and type of spasticity. (NA = not applicable, cases of familial spastic paraparesis).

ASIA		NEUROLOGICAL LEVEL		TYPE OF SPASTICITY
A	20 patients (22.2%)	C1-C4	21 (23.3%)	Tonic 57 (63.6%)
B	11 patients (12.2%)	C5-C8	30 (33.3%)	Phasic 5 (5.6%)
C	14 patients (15.6%)	D1-D6	15 (16.7%)	Mixed 28 (31.1%)
D	44 patients (48.9%)	D7-D10	8 (8.9%)	
E	1 patient (1.1%)	D11-L2	13 (14.4%)	
		NA	3 (3.3%)	

hospital). The dilution used was 1 ml physiologic saline solution. Muscle location was preferentially anatomic, though electric stimulation was occasionally used in deep or small muscles. Total doses were distributed by reference to patients' spastic patterns, in accordance with our recently published clinical practice guideline.[13] Whereas total doses of onabotulinum and incobotulinum ranged from 30-600 units and doses per muscle ranged from 15-200 units, total doses of abobotulinum ranged from 250-1750 units and doses per muscle ranged 50-700 units. Dose distribution depended on muscle mass and tone intensity.

- All statistical analyses were performed using the SPSS 12 computer software package, with values deemed statistically significant at $P < 0.05$. We used the Student's t-test for analysis of variables between 2 independent groups, and analysis of variance for a greater number of groups.

Results

A total of 90 patients were included in the sample; of these, 65 were men, mean age 41.92 years (range 18-77); in 58 patients the cause was traumatic (37 traffic accidents); 56.7% of injuries were cervical (mainly C4, C5 and C6, 39 patients in all), and 77.8% were incomplete (48.9% ASIA D). The mean SCIM III pre-injection score was 56.78 points (range 15-98).

In terms of type, spasticity was predominantly tonic in 57 patients and mixed in another 28, so that 56.7% of the sample had a PSFS score of 0-I; spasticity was focal in 47.8% of cases; the remaining patients presented with generalized spasticity but botulinum toxin was indicated because certain muscle groups were more affected or showed worse functional repercussions. Demographic data are shown in " Table 1". Noxious stimuli were found in 68.9% of patients (28.9% intestinal and 28.9% multifactorial). Spasticity was associated with articular limitations in 82.2% of patients and caused pain in 58.9%. Prior pharmacologic treatment was oral baclofen, isolated in 43 patients or associated with other drugs in 23 cases, 6 of whom required triple therapy.

Onabotulinum was used in 47 and abobotulinum in 41 patients. The injection site was in the lower extremities in 55.6% (the most infiltrated muscles are shown in "Figure 1"). A total of 23 patients received one-time treatment with BoNT, with treatment being repeated in the remainder.

Among the treated patients, mean muscle tone was 1.33, rising to 2.38 when only the injected muscles were considered; following injection, the mean fell to 1.18 points, with a mean improvement of 1.17 points. Improvement in tone, as measured by the MAS, was a mean of 1.3 points per muscle "(Table 2)". Goniometric improvement was achieved in 65.6% and improvement in pain in 38.9% of cases, while 87 patients reported that they had attained their functional goals (on the PGIC scale, 60% stated that the outcome was good, grades 1 and 2). The mean SCIM III score post-injection was 58.3 (15-98). A total of 8.9% of patients required no further treatment for spasticity. There were no adverse side-effects related with injection of and/or treatment with BoNT.

Patients with focal spasticity showed a significantly greater improvement in tone, goniometric performance, pain and function, in both the upper and lower extremities ($P < 0.0001$) as shown in "Table 2".

Men experienced a greater goniometric improvement ($P < 0.03$) and a more sustained effect after repeated injections ($P < 0.044$).

Although most of the subjects treated were chronic (with the first injection administered 6 months or more after onset in 72.2% of cases), it became clear that the earlier the BoNT injection, the greater the improvement in goniometric performance ($P < 0.006$) and pain ($P < 0.033$), with the best results being obtained within the first 6 months of clinical course.

ASIA D injuries showed a greater improvement in tone ($P < 0.0001$) and as can be seen in " Table 3" the effects were maintained for a longer period of time after each injection ($P < 0.01$).

Discussion

Use of BoNT to treat spasticity is officially accepted only when it is focal and due to stroke or cerebral palsy.[24,25] This means that most efficacy and safety studies exclusively target patients affected by these 2 disorders, namely, those for whom there is proven scientific evidence for use of BoNT.[30] In SCI, there are no studies of any type on the treatment of spasticity with BoNT: this treatment has only been studied in respect of sphincter dyssynergia,[31] and detrusor hyperactivity for which

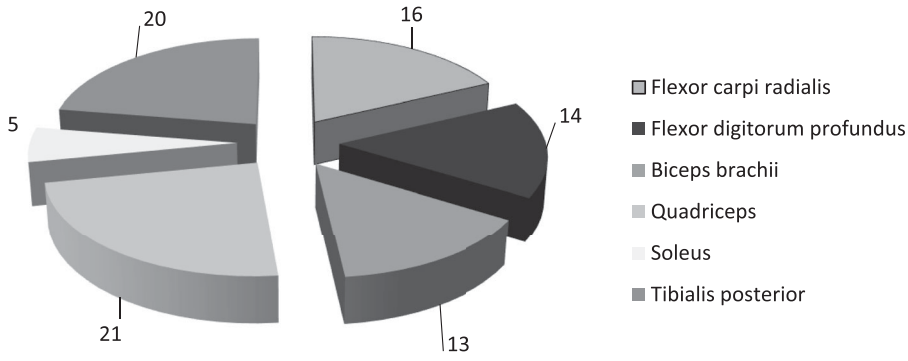

Figure 1 Muscles injected. Number of patients in which each muscle has been injected.

onabotulinum has enjoyed approved FDA indication since 2011.[32,33] Some BoNT indications that have not yet been approved by national or international drug agencies are contained in an international agreement, in which SCI-related spasticity is not included.[34] Hence, while BoNT could not be officially used, its use on a compassionate or off-label basis is suggested for spastic SCI patients in whom an indication can be found.[1,25]

Although indications for BoNT in SCI are somewhat limited by the generalized nature of spasticity, they are nonetheless described in certain cases in which spasticity is focal, especially in ASIA C and D spinal cord injuries.[35] Moreover, it may also be useful to apply BoNT to muscle groups that dominate the patient's overall spastic profile, either because they cause greater pain, or because they have worse functional repercussions.[7] In our study, patients who were treated displayed improvement in all study variables (tone, articular limitations, pain), tolerated the treatment well, and gave a positive subjective assessment. In corroboration of the general indications for treatment with BoNT, the patients who showed a significant improvement in our study were those who presented with focal spasticity.

In addition to the absence of clinical trials on the use of BoNT in SCI-related spasticity, there is remarkably little literature on the subject.[35] The papers that have been published report isolated cases or case series which may even mix different types of disorders or treatments. Consequently, systematic reviews of such studies furnish only one descriptive point of view without any scientific evidence,[36,37] and criticize the poor quality of the studies for failing to include functional or subjective improvements and making no mention of any side-effects that may have occurred. It was for this precise reason that we decided to report our unit's experience and summarize the main results.

The most extensive case series published to date was by Marciniak *et al.*,[38] which included 28 patients treated with BoNT/A (onabotulinum and abobotulinum), generally in the flexors of the upper extremities

Table 2 Differences between focal and generalized spasticity (ROM: range of motion).

	GONIOMETRIC IMPROVEMENT			IMPROVEMENT >2 IN VAS PAIN	
	NO	0-15°	COMPLETE ROM	NO	YES
FOCAL	11	10	22	19	24
GENERALIZED	20	16	11	36	11

	IMPROVEMENT IN PERFOMANCE OF FUNCTIONS OF UPPER LIMBS		IMPROVEMENT IN P'ERFOMANCE OF FUNCTIONS IN LOWER LIMBS	
	NO CHANGES IN SCIM III	IMPROVEMENT	NO CHANGES IN SCIM III	IMPROVEMENT
FOCAL	11	18	12	22
GENERALIZED	11	4	14	20

Table 3 Maintenance of improvement in tone according to AIS grade.

ASIA	MAINTAINED EFFECT	NOT MAINTAINED
A	9	11
B	8	3
C	13	1
D	36	8
E	1	0

and the antigravity muscles of the lower extremities, with treatment being solely applied in the first year of clinical course in 5 cases. Of the functional goals set prior to injection, 33% were attained in ASIA A spinal cord injuries, and 70% of those proposed for incomplete SCIs were likewise achieved. However, no significant differences in effectiveness were found between complete and incomplete SCIs, between upper and lower extremities, or in terms of a clinical course of more or less than 1 year. The failure to obtain any differences in this regard might perhaps be due to the fact that the sample of acute patients was smaller than that of the most chronic patients, though it has to be said that chronic patients also predominated in our sample, and significant improvements were achieved in acute patients. In our study, a significant improvement was observed in incomplete cases, and in ASIA D patients in particular, because the treated subjects had a higher percentage of focal spasticity. However, our study only took into account patients for whom treatment with BoNT was indicated, and not all the SCI patients attended. Accordingly, there is no way of knowing whether all incomplete patients have a higher likelihood of presenting with focal spasticity.

Other case series focus on hereditary or infectious spastic parapareses. In this connection, mention should be made of the series reported by Hecht *et al.*,[39] who describe 19 injected cases of familial spastic paraparesis (FSP), with improvement and side-effects, such as weakness in 4 cases and pain in 1, bearing in mind here that, in this type of lesion, the spastic pattern is flexor of the lower extremities. Other series with fewer cases were those reported by Bohlega[40] (which used a BoNT unavailable in Spain) and by Beseler,[41] which included 2 cases with other disorders.

There was one study of 15 incomplete patients with baseline and subsequent isokinetic assessments, in which only the rectus femoris muscles were injected with 200 U onabotulinum (Botox): the authors reported general improvement, though without specifying any details, as well as weakness in psoas in some cases.[42] The other series located had fewer than 6 patients,[43,44] while the remaining papers discussed isolated clinical cases.[45–,52]

The guideline used by us[13] includes a protocol covering all the evaluations that should be performed, both prior to and/or at the time of injection, as well as subsequently to assess results at 1, 3 and 6 months. However, completing the full series of medical visits often proved to be unfeasible because our hospital is a SCI referral center, and so many patients have to travel from some distance away and cannot attend as frequently as might be desirable. Across the clinical course, it was found necessary to extend the time of BoNT reinjection from 3 to 6 months or more, whether due to problems of geographic distribution, the greater duration of the effect after each injection, or the persistence of response to treatment in repeated injections, as described in the SCI literature.[43]

Study limitations. In view of the above, this study must be said to have certain limitations: insofar as possible selection bias is concerned, it only included patients who were referred to our hospital, and thus constituted a representative, though not uniform, sample of SCI at a national level; owing to their geographic dispersion, not all patients were able to complete follow-up; in terms of general indication, there is a preference for oral pharmacologic treatment over BoNT therapy; and finally, the study is purely descriptive, since there is no comparison of results versus placebo.

Conclusions

Botulinum toxin can be both an effective treatment for focal spasticity in SCI and a good coadjuvant for the other pharmacologic treatments in cases of generalized spasticity.

Treatment appears to be more effective in the first 6 months, and the subpopulations benefiting most from it are incomplete patients in general, and ASIA D patients in particular. Moreover, BoNT is a safe treatment, in that it has extremely few adverse reactions and is well tolerated by patients.

Further studies, especially clinical trials, are required to show the effectiveness of botulinum toxin in the treatment of SCI-related spasticity.

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